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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

CHIRON CORPORATION,

Plaintiff,

v.

ABBOTT LABORATORIES,

Defendant.

C 93 4380 MHP

EXPERT REPORT OF B. MATIJA PETERLIN, M.D. PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 26

I. QUALIFICATIONS

I am a Professor of Medicine, Microbiology and Immunology, at the University of California, San Francisco, and an Investigator, Howard Hughes Medical Institute at UCSF. My primary area of research has been focussed for the past ten years on the study of the molecular biology of HIV. A copy of my curriculum vitae is attached hereto as Exhibit A.

II. OPINIONS

A. Chiron's expression from the EcoRI-KpnI fragment from the ARV2 HIV[1] isolate resulted in an immunoreactive Env polypeptide.

Chiron's patent application No. 867,501 describes the identification, cloning and expression of the EcoRI-KpnI fragment from ARV2 in COS cells. We now know that this fragment contains open reading frames for Tat, Rev, Vpu, and Env (Gallo 1988). Staining with an AIDS antiserum revealed cytoplasmic fluorescence only in transfected cells ('501 Application, Sanchez-Pescador 1985). Subsequent reports by many investigators confirmed that this cytoplasmic staining was due to the expression of Env. These investigators also identified Env by electrophoretic mobility and immunoreactivity testing of lysates from these cells (Rekosh 1988, Bird 1990, Kimura 1994).

Schwartz et al., are the only group which did not detect the expression of Env with a fragment similar to the EcoRI-KpnI fragment from ARV2. In a HeLa cell expression system, they detected only Tat (Schwartz 1990). However, they expressed Env from the same fragment in the rabbit reticulocyte lysate, which is a different expression system. Schwartz et al. acknowledged that other investigators expressed Env with such fragments and were puzzled by their inability to do the same in HeLa cells.

Given the data in the Chiron patent and subsequent experiments from many groups, an ordinarily skilled scientist in 1984 or today could conclude confidently that the EcoRI-KpnI fragment from ARV2 expressed Env in COS cells.

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1 The virus that causes AIDS is now known as HIV, or human immunodeficiency virus. In 1984, when it was first isolated and characterized, it had several names given it by various research groups: LAV (by Dr. Luc Montagnier's group at the French Institut Pasteur); HTLV-III (by Dr. Robert Gallo's group at the National Institutes of Health); and ARV (by Chiron's collaborator Dr. Jay Levy at the University of California, San Francisco). The name "HIV" was established in 1986, and is used throughout this report for convenience (Coffin 1986).

B. An ordinarily skilled scientist in October 1984 could conclude that the peptide expressed from the EcoRI-KpnI fragment of ARV2 was from Env.

In October 1984, Tat, Rev, and Vpu were not known (Sanchez-Pescador 1985, Ratner 1985, Wain-Hobson 1985, Muesing 1985). An ordinarily skilled scientist following the example set out in the Chiron application would have expected to express Env and would have done so. By the intense cytoplasmic staining of transfected COS cells which is consistent with the presence of Env, the immunofluorescence test described in the application would have confirmed the expression of Env (Rekosh 1988, Bird 1990, Kimura 1994). Tat and Rev proteins have been localized to the nucleus and do not stain in the cytoplasm (Hauber 1987, Ruben 1989, Siomi 1990, Cullen 1988, Felber 1989, Hope 1990). Nuclear staining is easily distinguished from cytoplasmic staining in COS cells, which adhere to and spread out on glass or plastic support (Gluzman 1981). Once the immunofluorescence had confirmed Env, the product of the expression system could have been used by an ordinarily skilled scientist as a recombinant Env immunoassay in 1984. The presence (unknown at the time) of Tat, Rev, and Vpu along with Env would not have impeded the effectiveness of the binding of Env with an AIDS antiserum.

In the case of the ARV2, the cytoplasmic staining was due to the expression of Env alone. Vpu is an integral membrane protein, which contains 81 amino acids and measures 16 kDa (Cohen 1988, Strebel 1988, Maldarelli 1993). However, not only do many viral strains contain stop codons in *vpu*, but the ARV2 sequence as disclosed in the Chiron application contains a stop codon at position 38 in *vpu* (Sanchez-Pescador 1985, Cohen 1988, Myers 1994). Since all reported immunoreactive epitopes of Vpu are encoded by sequences beyond this stop codon (Schneider 1990, Kusk 1993), they would not be included in the protein expressed, and an AIDS serum would not recognize this truncated Vpu peptide from ARV2. Thus,

Chiron scientists did not express immunoreactive Vpu from the EcoRI-KpnI fragment of ARV2 in 1984.

An ordinarily skilled scientist working in 1984 with a viral isolate which contained full-length Vpu and Env would have expressed Env along with Tat, Rev, and Vpu (Rekosh 1988, Bird 1990, Kimura 1994). Although it was unnecessary to the recombinant Env immunoassay described in example 9 of the Chiron patent application, if an ordinarily skilled scientist had chosen to perform additional analysis on the product of the EcoRI-KpnI fragment expressed in COS cells, routine electrophoretic mobility and immunoreactivity studies of the expressed proteins would have both confirmed the presence of Env and distinguished Env from the unknown HIV proteins (Tat, Rev, and Vpu). The size of Env as indicated on the sequence of ARV2 in the Chiron application combined with the art in 1984 taught an ordinarily skilled scientist at the time that Env would be expressed as a large precursor and would be processed into two large polypeptides. Whereas Env polypeptides measure 160, 120, and 41 kDa, Tat, Rev and Vpu measure only 14, 19, and 16 kDa, respectively (Hauber 1987, Cohen 1988, Strebel 1988, Cullen 1988, Ruben 1989, Felber 1989, Hope 1990). In October 1984, as predicted by the ARV2 sequence described in the Chiron application, Tat, Rev, and Vpu would all have been demonstrably too small to be Env.

C. Plasmid vectors which could transcribe randomly generated short DNA fragments of unknown nucleotide sequence in all three open reading frames were available for the expression of HIV peptides in 1984 (Gray 1982). However, in October 1984, without accurate sequence information of the fragments and of the original viral genome an ordinarily skilled scientist would not have known from which part of the virus or the host genome these fragments arose.

D. In 1984, to generate recombinant polypeptides from Env of any HIV strain, an ordinarily skilled scientist would follow the guidelines of the Chiron patent application. The application states that other isolates of HIV can be found in

patients with AIDS or ARC. In 1984, methods for obtaining new isolates from lymph nodes or blood of patients were well known in the art (Barre-Sinoussi 1983, Gallo 1984, Schupbach 1984, Levy 1984, Luciw 1984). Indeed, the application teaches that two HIV isolates had been identified as of October 1984, one at the Institut Pasteur and the other at the Laboratory of Tumor Cell Biology at The National Institutes of Health (Barre-Sinoussi 1983, Popovic 1984). Two more viral isolates were characterized in the application (ARV3 and ARV4) and their sequences were described as being polymorphic. Thus, the Chiron patent application teaches that different isolates of HIV will have variability in sequence and that more viral isolates should be obtained and characterized.

Routine collaborations with hospitals serving communities in which the AIDS virus had been observed, as reported in medical journals and in publications such as Morbidity and Mortality Weekly Reports from the Center for Disease Control, would have and did yield sufficient patients and tissues to identify many new strains of HIV (Myers 1994). The Chiron application describes how to grow the virus in tissue culture cells and how to clone the viral genome. The application teaches that DNA hybridization will yield homologous sequences from new genomic or cDNA libraries. It also directs the sequencing of the viral genome, which was routine in 1984.

All HIV1 and HIV2 *env* sequences are sufficiently similar to permit the identification of their *env* ORFs with the HIV *env* probe described in the Chiron patent application (Myers 1994). Moreover, the amount of genetic diversity among *env* genes from various HIV1 and HIV2 isolates would not preclude an ordinarily skilled scientist from extrapolating the Chiron disclosure regarding the location of *env* in ARV2 to all other isolates of HIV1 and HIV2 (Clavel 1986, Guyader 1987, Myers 1994).

These steps have been followed since 1984, resulting in the rapid accumulation of viral strains and sequences as well as the identification of HIV2 and SIV (Clavel 1986, Hirsch 1986, Hahn 1987, Charneau 1994, Myers 1994). The

genomic organization of these lentiviruses, which was first outlined in the Chiron application, was confirmed. In HIV1 and HIV2, the location, size and features of *env* are maintained as are the strategies of viral replication and gene expression (Sanchez-Pescador 1985, Guyader 1987, Hirsch 1987). Therefore, an ordinarily skilled scientist could have followed the teachings of the Chiron application together with the art of 1984 to collect a variety of additional HIV1 and HIV2 isolates, to clone them, to sequence them, to identify and characterize their *env* genes, and to make and use recombinant Env immunoassays.

E. Dr. Jäck asserts that an inordinate number of disparate peptides from different strains of HIV would have to be examined to obtain smaller peptides to use as immunoreactive reagents against Env. Dr. Jäck does not explain how this assertion relates to the construction of a recombinant Env immunoassay in October 1984. If, for example, he means to suggest that his "hundreds of millions" of amino acid sequences must be examined to find short peptides which are broadly cross-reactive, he is wrong. In October 1984, an ordinarily skilled scientist would not have needed to take the approach suggested by Dr. Jäck to determine broadly cross-reactive short peptides. At the time, there were a number of well-known principles for predicting the immunoreactivity of a peptide (Sutcliffe 1983, Singh 1984). For example, instead of randomly expressing peptides from different strains of HIV, a small number of viral isolates would be sequenced and compared.

The Chiron application teaches that the three viral isolates from San Francisco were polymorphic, i.e., DNA fragments of different lengths were generated following their digestion with various restriction endonucleases. Following this observation, an ordinarily skilled scientist would have looked for differences in protein sequence between viral isolates in 1984. Routine examination of different Env sequences would have revealed hypervariable, variable, and conserved domains of the protein (Veronese 1985, Starcich 1986, Modrow 1987, Alizon 1987, Myers 1994).

Conserved sequences would then be examined for their hydrophilicity and hydrophobicity profiles and possible secondary structures (Sutcliffe 1983, Singh 1984). In the art of 1984, immunoreactive oligopeptides of predetermined lengths from conserved sequences were known to interact with specific antibodies (Laver & Air 1980, Wiley 1981, Benjamin 1984). Such routine approaches were in fact followed and yielded highly immunoreactive peptides from conserved regions of Env (Gnann 8/1987, Gnann 9/1987, Bugge 1990, Bottiger 1990, Krowka 1991, Sprengers 1991, Broliden 1992).

Based upon the teachings of the Chiron application and what was known in the art in October 1984, there was no need to screen hundreds of millions of variable sequences. The application identified *env* ORF, demonstrated its expression in cells, and demonstrated its polymorphism. Armed with this information, an ordinarily skilled scientist in 1984 could isolate and characterize new viral strains as well as predict, design and test the immunoreactive peptides from Env of HIV1 and HIV2.

F. It would not require extensive experimentation to express Env in host cells not known in 1984.

The Chiron application does not require the use of any specific expression system, or purport to claim the invention of expression systems. In October 1984, scientists of ordinary skill were routinely expressing heterologous genes in a wide variety of expression systems, including bacteria, plants, yeast, insect cells, and mammalian cells (e.g., Smith 1983, DiNocera 1983, Chernajovsky 1984, Old & Primrose 1985). After Chiron showed that Env expressed in mammalian cells was immunoreactive with an AIDS serum, an ordinarily skilled scientist would easily have combined the teachings of the patent with any of these expression systems known in 1984 or later to subclone the *env* fragment identified by the Chiron application into appropriate vectors and determine levels and fidelities of expression of recombinant proteins.

Moreover, Dr. Jäck is incorrect in stating that the expression systems he lists were not known in 1984. Most expression systems in use today were either known in October 1984, or are very similar in function to systems known in 1984. In fact, Chiron scientists and others have expressed Env in a variety of host cells and viral systems, including E. coli (Crowl 1985, Schneider 1987, Morikawa 1990), yeast (Barr 1987), baculovirus (Hu 1987, Morikawa 1990); CHO cells (Lasky 1986), COS cells (Sanchez-Pescador 1985), vaccinia virus (Chakrabarti 1986), and Drosophila cells (Ivey-Hoyle 1990). WOP cells and expression in sheep were not known in 1984. However, WOP cells represent a system analogous to COS cells (Kern & Basilico 1986, Ward 1994), and moreover, neither WOP cells nor expression in sheep has gained wide following in the field of gene expression.

G. In October 1984, a scientist of ordinary skill in the field at issue had an advanced degree (a masters, Ph.D., or M.D.) and experience in at least one of the three relevant technical areas: virology, immunology, or molecular biology, as well as some knowledge of immunoassays.

H. I have reviewed the opinions expressed by Dr. John Young in his report of May 1, 1995, and I agree with the conclusions expressed therein and the bases therefor.

III. COMPENSATION AND PRIOR TESTIMONY

I have not testified as an expert at trial or by deposition within the last four years. My compensation in connection with this matter is $270 per hour.

IV. INFORMATION AND REFERENCES CONSIDERED

In addition to Dr. Jäck's report and the references listed therein, and my experience in working in the field, as reflected in the publications listed in my curriculum vitae, I considered the content of the following list of articles and I have consulted with Dr. Young regarding the materials set out in Dr. Young's report at Section IV in forming my opinions. To exemplify the basis for the opinions set forth

above, I have referred to certain of these references in the text. These textual references are meant as examples, not as the exclusive support for each point.

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7. Barre-Sinoussi et al., "Isolation of a T-lymphotropic retrovirus for a patient at risk for acquired immune deficiency syndrome (AIDS)," Science 228: 868-871 (5/20/83).

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